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Disease-a-Month

Essential Hypertension

with Special Reference to Drug Treatment

ROBERT W. WILKINS

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Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

FIRST YEAR'S CONTENTS

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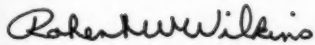

A graduate of Harvard Medical School, Dr. Wilkins in 1940 came to Boston University, where he is now Associate Professor of Medicine and a Member of the Evans Memorial Department of Clinical Research and Preventive Medicine, Visiting Physician, and Chief of the Hypertension Clinic, Massachusetts Memorial Hospitals. His publications are all on cardiovascular physiology and disease, beginning with "Beriberi Heart Disease" in 1936 and including studies on peripheral blood flow, hypertension and hepatic and renal blood flow. He is Vice President of the American Heart Association and President of the Massachusetts Heart Association.

HUMAN ESSENTIAL HYPERTENSION is a disease of unknown etiology, if indeed it has a single cause. However, most authorities agree that a number of different factors may play a role in its pathogenesis. These include (1) familial, (2) renal, (3) psychoneurogenic and (4) humoral factors. The roles of these various factors are not considered to be separate and independent of one another, but rather to modify and influence each other. For example, a hereditary tendency to hypertension is generally agreed to be transmitted from parents to children according to the mendelian law, but this tendency apparently manifests itself first, not as fixed hypertension, but as labile hypertension due to excessive neurogenic responses in pulse rate and blood pressure to stimulation. Thus, "prehypertensive" offspring of hypertensive parents, when subjected to ordinary stress such as cold, orthostasis or emotional stimulation, show more marked increases in pulse rate and blood pressure than do "normal" controls who have negative family histories for hypertension. Even the role of the *environment* of the family, as distinct from its

purely hereditary significance, is considered of importance in this connection, hence the use of the more inclusive term, "familial," to denote the possible psychogenic influence of family patterns of anxiety, aggressiveness and the like. Likewise, renal factors in hypertension, the importance of which is universally recognized, are generally regarded as probably operating through secondary humoral pressor mechanisms such as the renin-angiotonin system and vasoexcitor materials (VEM) or by influencing the body stores of sodium which in turn probably are regulated by adrenal cortical hormones. Most of these factors have been the subject of intensive investigation, particularly in animals. Although these studies are interesting and may in time fully explain the etiology and pathogenesis of certain types of experimental hypertension, the problems of the etiology and pathogenesis in different human beings will remain essentially clinical. These have been aptly described as a "mosaic" of factors which vary from one individual patient to the next and may be compared with the similar situation in cases of peptic ulcer.

TYPICAL COURSE OF ESSENTIAL HYPERTENSION

In spite of the individual variations from patient to patient, a fairly typical composite picture of essential hypertensive disease can be described. Thus, the typical case of essential hypertension begins in the young adult, age 30–40, and is usually quite asymptomatic, being discovered by accident on physical examination for life insurance, blood donation or induction into the armed forces. Characteristically, the pressure is merely labile at first, and often only a single elevated reading may be recorded under "basal" conditions for a period of years. The patient is inclined, or indeed has been urged by his physician, to ignore this lability of his blood pressure. It is recalled to his mind only when one (or both) parents has a stroke or a coronary accident or actually dies of "high blood pressure," or when the patient himself has intermittent symptoms that he may ignore at first, but which in time the astute physician will suspect as being hypertensive in

origin. These symptoms include, in order of frequency: (1) fatigue, (2) dizziness or "wooziness," (3) headache, particularly in the occiput or base of the skull, (4) palpitation, (5) dyspnea on exertion, (6) paroxysmal dyspnea especially at night, (7) nocturia, (8) blurring of vision. Frequently these symptoms appear only late in the course of the disease, when often the pressure has become "fixed" at a continuously high level. The serious complications, or more properly the consequences, of hypertensive vascular disease occur mainly in three regions: cerebral (including ocular), cardiac and renal. Typically, after a 20 year course the average case terminates at age 52, either with a cerebral accident, cardiac failure or, less commonly, renal failure.

The typical hypertensive patient is a woman, since women are twice as prone to develop the disease as men. However, to compensate, women tolerate the disease twice as well as men. She is usually a plump, pleasant, even a placid-appearing person but recognizes, and soon will express to the sympathetic physician, considerable inner turmoil and tension. She will even berate herself for these feelings and say that "little things" should not bother her as much as they do. If the patient be a man, he will smile a great deal, even when, as he may confess later, he is angry, because he has learned "it is worse to blow off than to hold in." He may or may not be aware of a marked conflict in his feelings of both dependence upon, and desire to dominate, someone close to him, usually his mother or wife.

The typical hypertensive is anxious, compulsive and perfectionistic. He is anxious about the future and particularly about his health. Having his blood pressure taken, or even discussing it, undoubtedly raises his pressure. He has many things that he feels he must do, such as being on time, being neat, clean and orderly; and he always likes to have things "just right." As a rule he sleeps poorly at night, and this distresses him so that he takes sedatives. Finally, the typical hypertensive is constipated and usually uses laxatives in order to insure a daily bowel movement.

In taking a *history* the physician should discuss the points just mentioned with the patient. Most significant are: (1) a positive

family history, (2) information about any previous elevation of pressure, as during pregnancy, (3) symptoms and signs of renal disease, (4) neuropsychiatric factors, such as financial reverses, and difficulty with wife, husband, parents or children, (5) specific symptoms of hypertension, including fatigue, headache, dizziness, dyspnea, nocturia and blurring of vision.

WORKING UP THE HYPERTENSIVE CASE

The most important single requirement in evaluating the patient with essential hypertension is time. This means not only adequate time in which to conduct the first interview, but adequate time for repeated interviews over an extended period. Only by obtaining in this way a running account or moving picture can one make a fair appraisal of the variability, severity and course of hypertensive disease. Careful and repeated history-taking should be done to bring out the factors already outlined. In addition, careful and repeated physical examinations should be made of the blood pressure, pulse rate, eyegrounds, heart size and sounds and the state of the lungs, abdomen and limbs, with emphasis particularly on signs of congestive heart failure. Of the laboratory studies, those bearing on renal function are the most important, including complete blood and urine analysis, phenolsulfonphthalein (fractional) test and measurements of blood nitrogen. A sedation test and cold and posture tests may be done to assess the degree of lability of the blood pressure. A chest x-ray and an electrocardiogram are made to reveal the degree of cardiac enlargement and pulmonary congestion. If indicated, a complete neurologic examination is carried out to detect minor or major cerebral accidents. The main purpose of these examinations and tests is to reveal the severity and course of the organic hypertensive cardiovascular-renal disease with a view not only to determining the therapy to be tried but to providing the background for judging its efficacy.

NATURE OF HYPERTENSIVE CARDIOVASCULAR-RENAL DISEASE

The only serious controversy raging in the field of essential hypertension today concerns the relation of the organic vascular disease associated with it. The points of difference arise over whether the vascular disease causes the hypertension, or vice versa; whether they are essentially independent but associated processes having nothing to do with each other in the ordinary individual patient, or whether, finally, they are different processes which unfortunately tend to aggravate each other. Autopsy studies of persons dying of hypertension leave little doubt that if the disease has been severe enough and lasting enough, there will be pathologic evidence of organic hypertensive cardiovascular-renal disease at death. On the other hand, renal biopsy studies of persons subjected to splanchnicectomy for early hypertension also leave little doubt that many persons with severe and "fixed" hypertension may have little or no renal vascular disease and therefore that these persons cannot be regarded as having "renal hypertension" unless this term includes functional as well as organic renal vascular abnormalities. Furthermore, clinical renal functional studies, which correlate remarkably well with the morphologic findings in these renal biopsies, suggest that many hypertensives have no significant derangement of ordinary renal functions or clearances. It is, of course, still possible that some renal function other than that measured by the usual tests may be found to be better correlated with the degree of hypertension.

The view which appears to be most consistent with the known clinical and experimental facts is that hypertension and "hypertensive" vascular disease are essentially different processes which, however, do ordinarily occur together and which can and usually do aggravate each other if they coexist long enough. Thus, hypertensive vascular disease, especially in the kidney, may aggravate the degree of hypertension, whereas hypertension, whatever its origin, may accelerate and aggravate vascular disease. It seems likely that both diseases have a similar familial incidence and

tend to occur together in the same patients. The most important consideration seems to be that hypertension is primarily a functional derangement and therefore is always (at least partially) reversible, whereas organic vascular disease is structural, and reversible only slowly if at all. These considerations support those who contend that therapy should be directed first at lowering the blood pressure, as soon and as much as possible, in order to retard the appearance of vascular disease, and that this should be continued as long as possible to arrest or even to reverse the course of established vascular disease. At least this latter therapeutic aims appears to be fully justified in advanced cases in which the combination of a high pressure and diseased arteries may lead to cerebral hemorrhages, or to cardiac decompensation, as a result of undue strain on organs so diseased that they cannot tolerate the increased pressure.

METHODS OF THERAPY

The older methods of therapy are well known and will not be discussed here in any detail. They include (1) diets, (2) surgery, and (3) psychotherapy. *Diets* are designed to limit the intake of calories, sodium or fats, or a combination of the three. Undoubtedly there is merit in limiting each of these in certain cases. Low caloric diets, if effective in reducing the body weight, relieve the load on the already overburdened heart; fat-free diets aid in this and also have the theoretical advantage of delaying the development of atherosclerosis. Sodium-free diets are the most efficacious type of dietotherapy in reducing blood pressure per se but are extremely monotonous, tasteless and difficult to maintain.

Surgery in the form of sympathectomy may be limited or extensive. If restricted, it appears to accomplish less than its maximum possible effect on blood pressure, but if too extensive it may so incapacitate the patient that he finds it difficult to work if not even to stand. A lumbodorsal splanchnicectomy appears to be about the optimum compromise between those undesirable extremes. Surgery has the great advantage that, once properly done,

it cannot be undone and is thereafter continuous in its effects night and day. On the other hand, it has the great disadvantage that in the individual patient no one can predict with certainty whether a beneficial effect will result from the operation. For a procedure as formidable and costly as this one, it is indeed a deterrent not to be certain of the results in advance. One fact which can be stated in extenuation of sympathectomy is that even when it fails to lower the "basal" levels of blood pressure, it usually relieves headache, lessens visual signs and symptoms and statistically prolongs life. Undoubtedly the production of postural hypotension by the operation may be partly responsible for these effects.

Psychotherapy at the minimum should consist of sympathetic interest and usually should include optimistic encouragement and reassurance. Emphasis should be laid on the favorable points in a patient's condition, with little stress placed on the actual level of the blood pressure or other unfavorable factors such as renal insufficiency, faulty vision or heart failure. In general, we prefer not to tell a patient what his blood pressure actually is. However, in some, who have been indoctrinated otherwise, not telling causes more anxiety than giving some figure. In the latter instance we may subtract 15–20 mm. from the correct readings.

Certainly a patient should never be told: "There is nothing to be done for your blood pressure." This is not only discouraging, it is untrue, since even a placebo enthusiastically prescribed makes the patient feel better and may actually lower the pressure significantly. Whether more thoroughgoing psychotherapy is worth while is highly problematical. Most internists feel that little is accomplished by psychotherapy beyond reassuring the patient and convincing him that the doctor is concerned, but certainly not worried or anxious, about the patient's condition.

Drugs

Because of the difficulties and the frequently unsatisfactory results of diets and surgery, drugs have naturally been tried for

hypertension. While various claims have been made for the "specificity" of one agent or another, all of the agents in common use today seem to be fairly nonspecific hypotensive agents if by that term it is meant that the drug in question does not correct some specific abnormality peculiar to the hypertensive patient but lowers blood pressure similarly in the normotensive as in the hypertensive patient. Only those agents which have proved to be efficacious and relatively safe when taken by mouth over prolonged periods of time will be discussed here, since it is considered that oral medications are greatly to be preferred to drugs given parenterally for long term therapy of any chronic disease. It seems fair to say that with the drugs now available there is a reasonable assortment of practical agents with which to begin the drug treatment of hypertension. Undoubtedly much better agents will appear in the future. However, even now, a thorough working knowledge of the modes of action and side effects of each of the currently used drugs, both alone and in combination with each other, and persistence in their use will lead to successful results in the majority of cases of essential hypertension.

SELECTION OF DRUGS.—It appears sensible to consider the several useful drugs in the order of their power to produce hypotension and to cause other physiologic, not to say pathologic effects. Table 1 gives such a listing.

Rauwolfia.—The mildest of the drugs both in its hypotensive action, which is slow and gentle, and in its side effects, which are essentially harmless, is rauwolfia and its various alkaloids. Of the latter, reserpine is the most extensively used and is one of the most potent, although it is not the only pure alkaloid of rauwolfia having hypotensive effects. Although the various available preparations and derivatives of rauwolfia are interesting from the chemical and pharmacologic point of view, their clinical actions are very similar whether they be a powder of the whole crude root, a total alkaloidal (alseroxylon) fraction or the pure alkaloid, reserpine. Various theoretical advantages may be claimed for one or the other, but as a practical matter, the question resolves itself into the factors of relative cost and personal pref-

TABLE 1.—Selection of Hypotensive Drugs for Oral Therapy

(In order of increasing severity of effects)

I. Rauwolfia serpentina

A. Forms and dosage
   1. Crude root powder: dose, 100 mg. one to four times daily
   2. Alseroxylon fraction: dose, 2 mg. one to four times daily
   3. Reserpine, pure alkaloid: dose, 0.1–0.25 mg. one to four times daily

B. Actions: Sedative, bradycardic, mild hypotensive, central (?)adrenergic blocking, increase of bowel motility

C. Undesirable side effects: Nasal stuffiness, gain in weight, depression, dreams

II. Veratrum

A. Forms and dosage
   1. Crude root powder or suspension: dose, according to animal assay
   2. Alkavervir fraction: dose, 2–4 mg. four times daily
   3. Protoveratrine (pure alkaloid): dose, 0.25–0.75 mg. four times daily
   4. Various alkaloids and mixtures of alkaloids: dose, according to animal assay

B. Actions: Central neurogenic vasodilator and vagal bradycardic agent

C. Undesirable side effects: Nausea and vomiting, arrhythmias, collapse

III. Hydralazine

A. Form and dosage
   Hydralazine hydrochloride: dose, 10–150 mg. four times daily

B. Actions: Central and peripheral adrenergic-blocking, general and renal vasodilator

C. Undesirable side effects: Cardiac stimulant, causes tachycardia and palpitation, and, in coronary disease, angina. Causes headache; may cause fever, arthritis, rash, "collagen disease"

IV. Hexamethonium

A. Form and dosage
   Chloride: dose, 31.25–750 mg. four times daily

B. Actions: Total autonomic ganglionic blockade, hypotension (especially orthostatic)

C. Undesirable side effects: Obstipation, postural hypotension, weakness, lack of visual accommodation, bladder atony, dry mouth, impotence, vasomotor collapse

erence of the patient and the physician. The situation may be compared with that obtaining with digitalis whole leaf and its various derivatives. For those who wish to prescribe by weight rather than by the method of animal assay, a pure chemical is preferable. However, in the case of rauwolfia, even more than that of digitalis, the clinical effects are so slow and gradual that one cannot be dogmatic concerning relative degrees of action of the different active preparations.

Rauwolfia has been taken for centuries in India as a tranquilizing or sedative agent, for which purpose it has been widely prescribed by Indian physicians, particularly in psychiatric cases. Indeed, it was in such cases that its peculiar hypotensive and bradycardic actions were first noticed. Rauwolfia is not a narcotic, in the sense that it will actually put one to sleep; rather, it calms or decreases the reactivity of both man and animals, especially lessening their aggressiveness and anxiety. Since, as already described, most hypertensives are prone to have these emotional reactions, and may even complain of them, the drug is particularly beneficial in allaying their irritability as well as other "neurotic" symptoms of which they may complain. These include "nervousness," "wooziness," headache, palpitation and insomnia. Since there is no evidence that it causes tolerance or addiction, rauwolfia apparently may be taken indefinitely without ill effects. This also makes it particularly suitable for use in a disease as chronic as essential hypertension.

As already mentioned, rauwolfia is a gentle, slow-acting hypotensive agent, requiring three to six days to produce any lowering of blood pressure and three to 10 weeks to produce its maximum effect. Similarly, when its administration is stopped one to six weeks may pass before its hypotensive action disappears. It also slows the pulse rate, but this slowing is usually not excessive and indeed may be quite useful, particularly when it occurs in a patient with tachycardia, either natural or the result of a tachycrotic agent such as hydralazine.

Because of its slow action, the effectiveness of rauwolfia as an agent for the treatment of hypertension should not be judged in

less than three and preferably six weeks of continuous administration. For this reason, physicians using it not only may, but perhaps should, not see their patients taking the drug oftener than every one to four weeks. Naturally, this implies that the patients are ambulatory and have relatively benign hypertension. Indeed, it is in just this type of patient, especially if he is also labile, neurotic and tachycrotic, that rauwolfia alone has its best effects. In this group of patients, rauwolfia is, in our opinion, not only the first agent to try but also the last to omit from a trial of medicinal therapy.

Rauwolfia may be given orally one to four times daily. The usual single starting doses are: of the crude root, 100 mg.; of the alseroxylon fraction, 2 mg., and of reserpine, 0.1 mg.; these doses are clinically comparable as nearly as this can be assayed in man. The time of dose may be suited to the patient's preference or to coincide with other combined medications. In addition, by varying the time of dose, the slight, relatively acute side effects of the drug can be suited to the individual patient's wishes. For example, if the patient dislikes too great a daytime sedative action, the whole dose can be taken at bedtime. If, on the other hand, the patient complains of vivid dreams or nightmares (a symptom of slight overdosage), this effect may be relieved by moving back the time of dosage to earlier in the day, oftentimes without reducing the total dosage.

The most common side effect of rauwolfia is nasal stuffiness. Many patients do not notice this, but in those with a small airway or chronic nasopharyngeal irritation, allergy or infection, it may be very objectionable. It tends to decrease in severity on chronic usage of the drug, and may be relieved in most patients by sprays or inhalations of vasoconstrictive substances or in some by oral medication with antihistamines. Presumably this symptom of nasal congestion is caused by vasodilation of the turbinates, since it is accompanied in many patients by easy bruising of the nasal mucous membranes, with flecks of blood appearing on vigorous blowing or wiping of the nose. While patients may think they have a chronic cold, characteristically the nose and throat

are dry, and an occasional patient may complain so bitterly of the dryness of the airway that he will stop the drug.

Rauwolfia has a definite tendency to cause a gain in weight. The reasons for this are not wholly apparent. Some patients claim that they have an increased appetite while on the drug; others insist that they do not eat more. Certainly the "slowing down" effect of the drug on excessive bodily activity is at least partly responsible. But whether the drug has more fundamental effects on metabolism is not clear. It does not appear to affect protein-bound iodine in the blood, but there are conflicting reports on its effects upon the ordinary basal metabolic rate. Our clinical impression is that the drug affects only the "nonbasal" metabolism, with the result that less energy is wasted in excessive "nervousness" and purposeless activity.

A third side effect of rauwolfia is increase of the motility of the bowel. This does not usually amount to diarrhea but is rather an increase in the urgency, if not the number, of fairly normal stools. This effect is usually welcomed by hypertensive patients who, as already stated, are commonly constipated. It is especially welcomed by physicians who are trying to use hexamethonium in hypertensive patients in whom this drug causes severe obstipation.

Another side effect of rauwolfia complained of by men, but not by women, is a decrease in libido. This is definitely a lack of sexual desire or interest, not impotence. It is noticed mostly by the middle-aged man who may be anxious about his virility. On the other hand, two young men have fathered new babies while taking the drug. Women have no change in libido, in menses or in other sexual characteristics while taking the drug.

The remaining side effects of rauwolfia are those of overdosage and can be easily relieved by interrupting or reducing the dosage. They include vivid dreams or nightmares and a state of trembly, weak, depressed anxiety. Patients in this state say they have the "jitters" and are "losing their grip." They usually have other signs of rauwolfia action such as definite bradycardia and hypotension, to suggest that rauwolfia is the responsible agent. These latter cardiovascular effects usually persist for some time

after the drug is stopped, whereas the jitteriness and depression quickly disappear.

While rauwolfia and its derivatives may be quite beneficial alone, particularly in relieving symptoms in the ordinary, labile, neurotic hypertensive patient with tachycardia, they find their best use as background or adjunct agents when the other more powerful drugs must be employed. Thus, not only do they lessen the reactivity of the individual, and decrease the disturbing side effects of the other drugs, but also by their own positive pulse-rate-slowing effect they counteract the tachycardia and palpitation of hydralazine, by their bowel-stimulating effect they lessen the obstipation of hexamethonium, and by their nausea-allaying effect they moderate the emetic action of veratrum.

Rauwolfia is also very helpful alone in maintaining a lower blood pressure in certain patients in whom this result has been achieved first by a combination of more powerful drugs, which then have been gradually dropped without a serious rise in pressure. Thus, the dosage of veratrum frequently, and of hydralazine occasionally, can be decreased or stopped altogether and the patient maintained simply on one dose of a rauwolfia preparation a day without a rise in blood pressure.

Finally, rauwolfia appears to be the ideal agent to try in patients who, on the basis of a strong family history, labile blood pressure and psychoneurogenic factors, may be strongly suspected to be "prehypertensives" if not early hypertensives. Physicians who feel that prevention or delay in the appearance of "fixed" hypertension in such patients should be attempted have welcomed rauwolfia preparations as practicable for this purpose, since these drugs are mild in action, do not cause tolerance or addiction and may be taken indefinitely without apparent harm. However, while there is no doubt that they will often maintain a continuously normal blood pressure in such cases, proof that their use in this "preventive" way is effective in prolonging life will come, if ever, only after very long term statistical studies.

Perhaps the most gratifying effect of rauwolfia preparations in typical hypertensive patients is the relief it gives of the com-

plaints characteristic of these persons. Prominent among these are palpitation, headache, anxiety, compulsiveness and irritability. Patients say: "I've lost the feeling that I *must* clean the house, now I can let a dish stay dirty at least until the next meal"; or "Little things don't bother me any more"; or "I can't remember when I've had a headache"; and "I don't know when I felt so good and relaxed." If there were no other beneficial effects of these drugs, the symptomatic relief that they bring most hypertensive patients would make their use worth while.

Veratrum.—Veratrum, like rauwolfia, is an old drug which recently has been variously repurified and prepared. Again from the clinical point of view, the several derivatives of veratrum appear to have little essential difference in action provided a carefully standardized preparation is used, whether this be crude root, alkaloidal extracts or pure alkaloids. However, since veratrum is considerably more dramatic in its effects than rauwolfia, it might be susceptible to more critical assay and has, therefore, somewhat greater likelihood of being prepared in a form clinically superior to those now available.

Veratrum is a neurogenic vasodilator which operates reflexly through the central nervous system to lower the blood pressure and slow the pulse rate. It does not block vasomotor responses or cause postural hypotension. Part of its action occurs through reflex vagal stimulation, but this may be blocked either by vagectomy or by atropine without abolishing its hypotensive action. Veratrum's most objectionable side effect is its strong tendency to produce nausea and vomiting. This action occurs at a dosage uncomfortably close to that causing hypotensive effects. As a result, patients taking the drug are liable to attacks of nausea and vomiting, which is a most unpleasant prospect for those on long term therapy.

Various preparations of the drug have been made in attempts to secure a greater hypotensive-to-emetic ratio. Although this apparently has been partially achieved in certain parenteral preparations, there is no convincing evidence that the goal has been attained for orally active derivatives. The most commonly used

preparations are relatively crude powders or suspensions, the purified "alkavervir" fraction, and the pure alkaloids, such as protoveratrine A and B and germitrine.

The drug is given three to four times daily because its duration of action is relatively short, namely, three to four hours. In general, it is more satisfactory if it is given in slightly larger doses at bedtime and breakfast than at noon and supper in order to compensate for the long interval during sleep at night. Some workers advocate giving only a single large dose a day, just short of the emetic dose, which results in a stronger but relatively brief single hypotensive reaction. In our opinion, evenly spaced doses three to four times a day are preferable, particularly if given in combination with other agents such as rauwolfia. As examples of starting doses, one could begin with 0.25 mg. of protoveratrine or 2 mg. of the alkavervir fraction, four times a day (at meals and at bedtime), slowly increasing the doses (first the bedtime, then the breakfast and finally the noon and supper doses) until a relatively smooth hypotensive effect is achieved or premonitory symptoms of nausea ("heartburn," "indigestion" or excessive salivation) are produced.

There is considerable evidence that a sort of resistance to veratrum develops in patients taking the drug chronically. This is not a true resistance in the sense that the drug ceases to act altogether; rather it is the development of an "all or none" reaction in the sense that the patient has little or no hypotensive effect until the dosage is raised sufficiently to cause a marked drop or even a collapse of the blood pressure, along with severe nausea and vomiting. As already mentioned, patients are inclined to take a dim view of continuing on doses of the drug likely to produce such reactions. In any case, the drug after a month or so of continuous dosage is usually considerably less satisfactory than it was initially.

Aside from nausea and vomiting, veratrum has few serious side effects. It can cause cardiac arrhythmias, particularly ventricular premature beats, which in association with the strong vagal stimulation and bradycardia may cause considerable palpitation. In

addition, in excessive dosage it may cause varying degrees of auriculoventricular block. Both types of disturbance frequently may be relieved by atropine. In overdosage sufficient to produce a severe hypotensive reaction, veratrum can cause apparent collapse of the circulation, particularly in the upright position. However, although occasional patients have fainted in such reactions, so far as is known none have died, and, indeed, veratrum, next to rauwolfia, may be said to be the safest of the oral hypotensive drugs.

As mentioned previously, veratrum may be used successfully in combination with other hypotensive drugs. Foremost among these is rauwolfia, which not only seems to potentiate the hypotensive effect of veratrum but also to make larger doses of veratrum tolerable to the patient without producing nausea and vomiting. Veratrum may also be used in conjunction with hydralazine, particularly when rauwolfia has not been adequate in its bradycrotic effect to control the pulse at a rate under 80 beats per minute. For this purpose, veratrum is usually added to the rauwolfia, and when the pulse rate is brought below 80, if a further hypotensive effect is still desirable, hydralazine may be added as a third agent.

Hydralazine.—Hydrazinophthalazine is a new synthetic chemical having unique renal vasodilating and blood-pressure-lowering properties. It also has certain peripheral adrenergic blocking effects, but in chronic clinical usage these are usually not apparent in the form of postural hypotension or other disturbances of vasomotor reflexes. Indeed, most of the common, acute, objectionable side effects of hydralazine, such as headache and palpitation, disappear on chronic use, which makes the drug clinically much more acceptable than it otherwise would be. This is particularly true if the drug is instituted in small and gradually increasing dosage or is used in combination with a moderating drug such as rauwolfia.

In addition to peripheral blocking effects, hydralazine has certain central nervous adrenergic blocking actions, particularly on reflexes operating through the midbrain. Whether or not these are clinically important is not clear. It is interesting that one

symptom, nasal congestion, resembles that caused by rauwolfia, which also acts on the midbrain. The most apparent of the early actions of hydralazine subjectively and objectively are those on the heart, which it stimulates strongly, increasing both the heart rate and the cardiac output markedly. These effects lead to the frequent complaint of palpitation and also probably are responsible for the production of angina pectoris, particularly in persons suspected of having coronary disease.

Hydralazine is a hydrazine derivative and as such might be expected to have the toxic effects of synthetic chemicals containing benzene rings. However, as far as is known, only one case of bone marrow depression with pancytopenia has resulted from taking this drug. This effect disappeared promptly when the drug was stopped. Other relatively early toxic side effects of the drug are nausea, fever, tingling of the extremities, arthralgia, leukocytosis and rashes. Peripheral dependent edema, a common early side effect, may not be "toxic" but rather may be the result of peripheral adrenergic blocking effects, which produce edema in a manner similar to that occurring early after a peripheral sympathectomy. Most of these early symptoms tend to disappear with continued use of the drug, but a serious rash or a fever is adequate cause for discontinuing its use.

The most serious toxic side effects of hydralazine occur late (several months) after its continued use and consist of a "lupus erythematosus-like" collagen disease. Thus, a patient may begin to complain of arthralgia or actual arthritis with swollen, tender joints, and he may have a rash, fever, anemia, increased albuminuria, a positive cephalin flocculation test and even LE cells in the peripheral blood. Such reactions have almost always occurred in patients taking sizable doses of the drug (over 200 mg. a day) and showing notable improvement in blood pressure as a result of the therapy. Any of the afore-mentioned late symptoms constitute adequate reason for stopping the drug and never reinstituting it. In our experience, this results in a prompt remission in this strange disease.

Hydralazine is perhaps the most useful of the stronger drugs in

lowering blood pressure in moderate to severe hypertensive cases. This is particularly true when it is used in conjunction with a rauwolfia preparation. It seems to be particularly efficacious in lowering the diastolic pressure, denoting its general as well as renal vasodilating action. The hypotensive effect of the drug is often quite dramatic, particularly when the critical dosage level is reached, at which point the addition of as little as 25 or 50 mg. a day may "break" the pressure from its previously "fixed" high values to a definitely lower range. When such a "break" occurs, the same dosage should be continued for several weeks during which time a further gradual moderation of pressure often occurs.

It is generally agreed that hydralazine should be given several times daily; we ordinarily employ the four dose schedule for this as for all hypotensive drugs taken orally. The starting dose of hydralazine should be small, i.e., 10–25 mg. four times a day, with instructions to halve even that dose if intolerable symptoms such as headache or palpitation appear. The patient should be cautioned against actually stopping hydralazine and should understand that the aim is gradually to increase the dose so as to accommodate himself to the drug. This plan, along with a "background" preparation with rauwolfia for several weeks, or at least an accompanying moderating dose of rauwolfia, will usually allow hydralazine to be instituted relatively smoothly, at least without intolerable discomfort.

An occasional patient will appear to be completely unable to take hydralazine. Usually this is because of headache, palpitation or both and characteristically occurs in persons with a low threshold for pain or discomfort. In such patients, analgesics should be used for the headache, along with reassurance that it will pass off. As for the palpitation, one may often avoid this by not giving hydralazine when the patient already has tachycardia, but rather first giving rauwolfia, veratrum or both, to lower the pulse rate below 80. Hexamethonium used in conjunction with hydralazine also moderates its cardiac stimulating and pulse-accelerating effects.

The most serious cardiac complication of hydralazine medication is the production of angina pectoris with adverse electrocardiographic changes in persons with known or suspected coronary disease. This complaint resembles status anginosus more than angina of effort and characteristically consists of a fairly continuous substernal aching or soreness which is not particularly related to exercise, excitement, meals or exposure to cold. In a trial of patients with this complaint or with known angina of effort, we found that hydralazine intravenously produced the pain and adverse electrocardiographic changes in every one, whereas the Master two-step test failed to do so in some. However, we do not recommend the intravenous administration of hydralazine as a clinical test for coronary disease, since we consider its effects in such cases to be deleterious. This hydralazine angina is apparently due primarily to the stimulation of cardiac output and the resultant increased myocardial work in persons whose coronary circulation cannot dilate to compensate for the added load. It may occur without a decrease in blood pressure, differing in this respect from the angina occurring in patients taking hexamethonium which, in our experience, always appears during marked hypotensive reactions. The appearance of angina in patients on hydralazine is considered to be adequate cause for markedly reducing, if not omitting, this agent from the medicinal regimen for hypertension.

Hexamethonium.—Hexamethonium is a total ganglion-blocking drug and in adequate doses is capable of inhibiting all autonomic reflexes, whether sympathetic (adrenergic) or parasympathetic (cholinergic). Therefore its actions are widespread, and to one interested solely in obtaining its hypotensive action many of these blocking actions may appear to be adverse side effects. Actually, the drug may be said to have very few if any really "toxic" effects, if one discounts the relatively rare cases of interstitial pneumonitis that have occurred after chronic usage of large doses. Nevertheless, because it is so very potent and blocks so many important reflexes, it is the most difficult, and troublesome, if not actually dangerous, drug used for therapy of hypertension.

Hexamethonium has some particularly unfortunate dosage characteristics for a drug so potent and widespread in its actions. Thus, the dosage may vary from patient to patient, and even in the same patient from time to time, by several hundred times. Part of this wide dosage range is due to the rapid development of tolerance to the drug. Therefore, the only safe procedure is to start a new patient with an extremely small dose, observe its acute effects and to increase the dosage until at least postural hypotension or adverse symptoms of some other type appear. This method of dosing is known as "titrating," by which it is meant that increments are added to the dosage until a definite physiologic effect appears.

Fortunately, in the usual hypertensive patient, a fall in blood pressure, at least in the upright position, is one of the early physiologic effects of an active dose of hexamethonium. When this is achieved the physician should be very cautious about increasing the dose and tend to continue this same dosage on a four-dose schedule, giving the drug *before* meals and at bedtime. Thus, when it has been decided that hexamethonium must be tried, and in our opinion it should never be tried until this is proved to be necessary (usually by the failure of any other combination of drugs to achieve a therapeutic result), hexamethonium is instituted in an initial oral dose of 31 or 62 mg. (one-quarter to one-half of the 125 mg. tablet). The patient remains reclining, and blood pressures are taken at five to 15 minute intervals, in the lying, sitting and standing positions for 1½ to two hours and thereafter at half hourly intervals. If no blood pressure (or other autonomic blocking) effect is seen, the dose may be doubled on the next administration four to five hours after the first, and the same blood pressure observations repeated. This "titration" is continued until a hypotensive or other effect is achieved, or the single dosage reaches 500–750 mg. When a hypotensive effect is obtained, that dosage is maintained, or, as usually is necessary, with the development of tolerance the dose is raised gradually so as to continue the hypotensive effect.

As already mentioned, hexamethonium has other autonomic blocking actions that must be reckoned with. Foremost among them is constipation, not to say obstipation or paralytic ileus. This effect must be counteracted so that the patient will have a daily bowel movement, or the intestinal absorption of the drug will become so erratic as to make its use impossible. Any moderate cathartic which works will do; we have come to rely on a mixture of half mineral oil and half milk of magnesia at bedtime in a dosage adequate to produce a morning movement. If this is not obtained, cleansing or stimulating enemas must be resorted to.

Other objectionable side effects of hexamethonium include weakness and giddiness, which are related in part to the hypotension, especially the postural hypotension, that it causes. Fuzzy vision due to lack of accommodation, dry mouth and throat due to blocking of salivary reflexes, difficulty in urinating due to bladder atony and impotence due to lack of erection are also prominent. Fortunately, most of these effects diminish with continuous use of the drug, but needless to say they do not endear hexamethonium to either the patient or the physician.

Some of the side effects of hexamethonium, or at least the patient's reaction to them, may be lessened by the simultaneous administration of a rauwolfia preparation. Thus, constipation in particular is counteracted by the bowel-stimulating effect of the latter drug. Rauwolfia not only counteracts or lessens the patient's irritation at some of the objectionable features of hexamethonium but, by acting additively if not synergistically with its hypotensive effects, lessens the necessary dosage and hence the side effects, of hexamethonium without losing its blood-pressure-lowering effect. Hexamethonium is used most often in combination with hydralazine, with which it constitutes the most potent drug attack on hypertension. Even for this purpose, however, the treatment is smoother and the necessary dosage of the two drugs is smaller if rauwolfia is also used as a third drug in the regimen.

Other total ganglionic blocking drugs such as pentapyrrolidinium and SU-3088 have certain differences from and certain theo-

retical advantages over hexamethonium, which has been discussed here as the prototype of this group. Their physiologic actions and clinical effects are essentially similar to those of hexamethonium, although in occasional patients they may be effective when hexamethonium has failed. However, much more work is required before they can be proved to be definitely superior to that drug in the average patient over long periods of time. Claims to the contrary usually fail to take into account the fact that clinical experience with any of these powerful drugs not only is indispensable in their own use but may be of great value in the use of a new analogue. Hence one may question whether the better results reported initially with a new drug are due to real improvements in the drug or to the greater skill of the physician who has had previous experience with a similar agent.

Plan of Drug Treatment

Using the four agents that have just been described, rauwolfia, veratrum, hydralazine and hexamethonium in that order, adding the next drug to the regimen only if necessary (and if tolerated), the physician can follow a general plan of treatment in practically every case of hypertension. In this plan, the treatment is suited to the patient on a trial basis. Thus, in the ordinary uncomplicated case of essential hypertension, the patient is started on rauwolfia, 100 mg. of the crude root or its equivalent in the form of a purified fraction or pure alkaloid. This dose is given one to four times a day or, preferably, started once a day and increased, if necessary, to four times a day. It should be stressed that on a single daily dose of this type, about half of the early cases, especially the labile cases with tachycardia, will respond within one to four months with a fall in blood pressure to or nearly to normal and a fall in pulse rate to below 80 beats per minute. Obviously, therefore, no patient should receive more potent therapy until this is proved necessary.

Unfortunately, there is no certain method of predicting in ad-

vance which patients will and will not so respond. In general, it can be stated that those with more extensive cardiovascular renal disease will require stronger therapy. However, not infrequently a patient with little or no organic cardiovascular disease and mild, labile hypertension with tachycardia will fail to respond, whereas another one with serious organic disease, "fixed" hypertension and bradycardia will show a dramatic response to rauwolfia alone. It is worth noting here that patients with "renal" hypertension, i.e., hypertension associated with known renal disease such as pyelonephritis or polycystic kidney disease, may respond as readily and as well to drugs as those with "essential" hypertension.

If, after several weeks of trial rauwolfia alone is not sufficiently effective in lowering the blood pressure, a second drug is added. Generally, this drug is hydralazine, since the pulse rate usually has been slowed by rauwolfia to below 80, making hydralazine less likely to produce palpitation. Occasionally the second drug to be added to the schedule is veratrum, particularly if the pulse rate is still elevated above 90 beats per minute. In either case the patient is placed on a four dose schedule (at meals and at bedtime), and the dose of the added drug is increased until hypotensive effects or adverse symptoms appear.

If, after a period of weeks two drugs in combination are ineffective, the third is added, again in gradually increasing doses. In the case of hydralazine, the total dosage is raised to 400 mg. a day or even to, but never above, 600 mg. a day. If such a dosage in combination with the maximum tolerable doses of rauwolfia and veratrum does not lower the pressure, or if toxic side effects of hydralazine occur, a decision must be made as to whether to try hexamethonium. This decision is based not solely on the blood pressure levels but also on the severity of the associated cardiovascular renal disease and especially on evidence of its rate of progression. Obviously, if the course is judged to be malignant, with papilledema and fresh hemorrhages in the retinae, hexamethonium is more likely to be used. Similarly, if there is intrac-

table or progressive heart failure which has not yielded to digitalis and diuretics, the use of hexamethonium should be considered. If, on the other hand, there is severe uremia, the administration of this agent should be undertaken with great caution, if at all, since it is eliminated by the kidneys and may accumulate rapidly in dangerous amounts when renal function is markedly impaired. The occurrence of repeated cerebral accidents also affects the decision as to whether to try hexamethonium. If these accidents are clearly hemorrhagic and presumably the result, at least in part, of excessively high pressures, one may be justified in starting the drug. If, on the other hand, the accidents are clearly thrombotic, one may hesitate to induce sudden hypotensive episodes with hexamethonium for fear of causing similar thromboses.

Hexamethonium therapy is usually instituted in the hospital, although in intelligent patients who are well indoctrinated in the use of hypotensive drugs, it may be started on an ambulatory basis. The patients should be thoroughly warned of its side effects, particularly concerning the postural hypotension and the danger of fainting in the upright position. They should be cautioned to sit down or lie down whenever they feel faint or dizzy and not to try to "stick it out." They should also be instructed to avoid constipation.

Unless the patient is a doctor or nurse or the relative of such a professional person, he is usually not asked to record home blood pressures or to try to manage his dosage according to the levels of blood pressure. There are at least two reasons for this: (1) the anxiety that such attention to blood pressure readings causes appears to us to have a bad emotional impact, and (2) patients tend to change or reduce medications at the slightest deviations in their pressures. In addition, we feel that the less inconvenience and notice caused by a medicinal regimen the more successful it will be, everything else being equal.

Once an even moderately successful hypotensive regimen has been established in a patient without any, or very serious, side effects, the physician should rest on this schedule for at least a

period of weeks. Often, merely persisting longer with such a therapeutic effort will result in a further gradual, and occasionally sizable, reduction in pressure. Such persistence, perhaps more than any other single quality, is responsible for success in this type of therapy. The attitude of the physician should be, on the one hand, not to accept defeat in his efforts to lower the pressure but, on the other, to be content with moderate or gradual success as long as it continues.

When, as happens in at least two thirds of the cases, blood pressure has been definitely reduced for several months, the physician should turn his attention to the possibility of reducing or even omitting such dosages of drugs as can be accomplished without a rise in pressure. If the pressure is essentially normal and veratrum is a part of the regimen, this drug can usually be omitted without a rise in pressure. Next, an attempt should be made to reduce the dosage of hydralazine because of its possible toxic effects which appear to be partly dose-connected. While this drug can only occasionally be omitted altogether without a rise in pressure in a patient in whom it has had a dramatic effect, the dose can often be reduced to less than 200 mg. a day, which rarely if ever causes chronic toxic effects. Hexamethonium dosage also can be reduced, if not omitted, in many patients, particularly if rauwolfia is continued. Hexamethonium should never be wholly omitted suddenly, in order to prevent the occurrence of rebound overshoots of pressure that occur occasionally with fatal results on stopping this drug. If the drug is omitted inadvertently, even for a day or two, it should be reinstituted in a smaller dosage than had been used before, because a patient may rapidly lose his tolerance for this drug and have an excessive hypotensive response when the same dose is readministered.

In no case of successfully treated, previously "fixed" hypertension have we been able to omit hypotensive drug therapy altogether. In every case at least a small amount of a rauwolfia preparation has been required to prevent a rise in blood pressure. In some patients, the amount of drug necessary to maintain the

hypotensive result has been extremely small, e.g., 0.05 mg. of reserpine a day. Although it is disappointing that a "cure" by drugs does not seem possible with the agents presently available, it is encouraging that in a patient susceptible to hypertension a reduction in pressure appears to be easier to maintain than to initiate, especially after the pressure has been "fixed" at a hypertensive level for some time. The implications of this concept from the point of view of pathogenesis of the disease are fascinating, since they suggest that the body gradually accommodates itself to a certain blood pressure level which it defends with a battery of homeostatic mechanisms tending to maintain that level. If one visualizes the fundamental fault in hypertensive patients as a familial "tendency" to elevated blood pressure when under stress, then one can consider drug therapy as a counteracting "tendency" toward lower blood pressure. Since the former tendency is probably inherent, not to say inherited, the latter tendency must be equally continuous and sustained to be effective.

SUMMARY AND CONCLUSION

Orally effective drugs are now available for trial by the physician who feels that he should treat patients with hypertension. They include, in order of their increasing power, both to decrease blood pressure and to produce objectionable side effects: rauwolfia (the mildest), veratrum, hydralazine and hexamethonium (the severest). These drugs almost certainly do not represent the ultimate in this field of chemotherapy; rather, they are but as "sulfanilamide to penicillin."

A thorough working knowledge of the main actions and side effects of each drug is, of course, essential. However, their use, especially in combination, is not prohibitively difficult and can be carried out on an ambulatory basis. This requires persistence, patience and careful supervision of their administration, beginning with a trial of the mildest drugs first, adjusting ("titrating") the doses and rearranging the schedules so as to give the maximum

benefit with a minimum of disturbance to the patient. This type of management may be likened to that of chronic peptic ulcer or even chronic valvular heart disease, in which drugs, diets, regulation of occupation, habits and emotional reactions, and even surgery, may be considered as possible therapeutic approaches.

The physician undertaking this type of management should regard each new hypertensive case as a challenge, in which he will simply not accept defeat. Although it is impossible at present to effect a "cure" in the sense of restoring the patient completely to normal with no further attention to the disease, it is possible in all but terminal cases to decrease the blood pressure without interfering too seriously with the patient's life. The minimum objective of the physician, in this as in all other diseases, should be to make life more pleasant. Therefore, therapy that causes serious symptoms cannot be considered satisfactory, whatever its effects on blood pressure. Fortunately, however, the newer drugs, especially rauwolfia, offer at least symptomatic relief to the ordinary hypertensive patient.

Rauwolfia lessens considerably the objectionable side effects of the more powerful drugs. It is used routinely in every case, at least as a "background" agent. In about one half of unselected office-type ambulatory hypertensives, it is satisfactory alone. Therefore, the stronger drugs should be added to it only if rauwolfia does not produce a satisfactory response within six weeks, or even within a somewhat shorter period in cases severe enough to warrant urgent treatment with a full battery of agents.

Of the stronger agents, hydralazine, although most useful, is most likely to cause "toxic" reactions, while hexamethonium, although most powerful, is most likely to cause serious physiologic reactions. Therefore, their use should be undertaken only with due respect for their powers. Nevertheless by carefully indoctrinating patients as to the nature of the drugs and by warning them of the symptoms of untoward effects, the physician can successfully employ even these stronger agents on an ambulatory basis. Always, however, he should reserve them for use only when

proved necessary; and he should try to reduce or omit them in a regimen that he expects will have to be maintained indefinitely.

In conclusion, it may be said that while the drugs now available for hypertension have not simplified the physician's management of that disease, they have increased enormously his satisfaction in treating it, because they have enabled him to induce not only subjective but also objective improvement in many hypertensive cases about which he previously felt helpless, not to say hopeless.